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Perioperative Erythropoietin Administration in Patients With Gastrointestinal Tract Cancer

Prospective Randomized Double-Blind Study

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Objective
To investigate the effect of recombinant human erythropoietin (r-HuEPO) administration on perioperative hemoglobin concentrations and on the number of blood transfusions in patients undergoing surgery for gastrointestinal tract malignancies.

Summary Background Data
Erythropoietin has been shown to improve the yield of autologously predonated blood and to reduce the subsequent requirements for homologous blood transfusions in cancer patients.

Methods
In this double-blind placebo-controlled study, 31 cancer patients received subcutaneous r-HuEPO in a dose of 300 IU/kg body weight plus 100 mg iron intravenously (study group) and 32 patients received placebo medication and iron (control group). All patients received the medications daily for at least 7 days before and 7 days after the operation.

Results
Patients who received erythropoietin received significantly fewer transfusions intraoperatively and postoperatively. Postoperatively, the study group had significantly higher hematocrit, hemoglobin, and reticulocyte count values compared to the control group. The use of erythropoietin was also associated with a reduced number of postoperative complications and improved 1-year survival.

Conclusions
Patients with gastrointestinal tract cancer and mild anemia benefit from perioperative erythropoietin administration in terms of stimulated erythropoiesis, reduction in the number of blood transfusions, and a favorable outcome.

Allogenic blood transfusions have been reported to be associated with a high cost, higher perioperative morbidity, and higher recurrence rate in patients with gastrointestinal tract cancers. Several attempts have been undertaken to reduce the use of blood transfusions by initiating autologous blood transfusion programs.[1–7] Erythropoietin has been used, in an experimental manner, to improve the yield of autologously predonated blood and to reduce the subsequent requirements for homologous blood transfusions, especially in orthopedic and colon cancer patients.[5,8]

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In cancer patients, possible causes for anemia include bleeding, nutritional deficiencies, hemolysis, and suppressed hematopoiesis. Furthermore, inappropriately low levels of endogenous erythropoietin, lower than in patients with iron deficiency anemia at comparable hemoglobin values, have been reported.[9–11] To study the effect of exogenous perioperative erythropoietin administration in reducing the need for heterologous blood transfusions in cancer patients, we performed this prospective double-blind randomized study.

METHODS

Between January 2000 and May 2001, 75 patients with nonmetastatic cancer of the gastrointestinal tract treated in

the A' Department Of Propaedeutic Surgery of Athens Medical School were included in the study. The study inclusion criteria were a diagnosis of nonmetastatic gastrointestinal malignancy (stomach, 15; colon, 38; rectum 22), age between 40 and 90 years, and moderate anemia (hemoglobin values 8.5–13 g/dL). Exclusion criteria included severe concomitant disease, history of thromboembolic disease, pregnancy, history of hepatic or kidney dysfunction, systemic hematologic disease and blood transfusions within 30 days before surgery, or hemoglobin values more than 13 or less than 8.5 g/dL.

Patients were randomized either into the study group, receiving 300 iv/kg body weight Epoietinum Alfa (Janssen-Cilag AG, Europe) subcutaneously each day, or into the control group, receiving placebo medication. All patients were given 100 mg iron (Venofer, Switzerland) intravenously each day. Erythropoietin or placebo applications were given for 14 days perioperatively, starting 7 days before the operation. Patients received the regimens on an outpatient basis. The regimens were administered and blood samples were obtained in our 1-day clinic, where patients were admitted for 2 hours in an outpatient manner while remaining under continuous surveillance for possible adverse effects. Informed consent was obtained from all patients. Both patients and investigators were blinded for the performed application.

Intraoperative blood loss was estimated by the amount of blood collected in the aspirator and by the weight of the gauzes used. The indication for blood transfusion was a hemoglobin value of 8.5 g/dL or less. In all patients, blood cell counts and serum chemistries were performed every second day until discharge. In addition, reticulocytes, ferritin, and iron were measured at admission, the day of operation, and at discharge.

Patients and Data Management

In a 16-month period, we enrolled 75 patients in the study. Twelve randomized patients were excluded from the study because they did not fulfill the inclusion criteria. Two had had blood transfusions within 1 month before study, four dropped out for personal reasons, two were excluded due to protocol violation, and four were proven at operation to have distant metastases.

Table 1. CLINICOPATHOLOGIC DATA

	Study Group	Control Group
Patients (n)	31	32
Age (years) ± standard error of the mean	67.1 ± 2.1 (median 70)	66.4 ± 2 (median 66.5)
Male/Female	15/16	19/13
Tumor location		
Stomach	6	7
Colon (R/L/R + L)	18 (7/9/2)	15 (8/7/0)
Rectum	10	9
Type of operation		
Gastrectomy (total/subtotal)	6 (5/1)	7 (3/4)
Colectomy	25	25
Low anterior	6	5
Right	5	8
Left	9	7
Subtotal	2	0
Abdominoperineal resection	3	5

Statistical Analysis

The Student *t* test was used to compare means of measures. The paired sampled *t* test was used to compare values of hematocrit, hemoglobin, and reticulocytes in all the patients in different time points. Chi-square and Fisher exact tests were used where applicable. The Kaplan-Meier curve was used for univariate survival analysis, while outcome measures were evaluated using a multivariate Cox regression analysis. Statistical significance was achieved at $P < .05$.

RESULTS

Randomization

Sixty-three patients were randomized, 31 (49.2%) into the study group and 32 (50.8%) into the control group.

Table 2. HEMATOLOGIC PROFILE

	Study Group	Control Group	*P* Value
Hemoglobin at admission (g/dL)	10.6 ± 0.18 [11]	11.1 ± 0.19 [11]	.11
Hematocrit at admission (%)	33.5 ± 0.5 [34]	35.2 ± 0.6 [34]	.054
Reticulocytes at admission (%)	1.5 ± 0.1 [1.2]	1.58 ± 0.2 [1.1]	.7
Iron at admission (mg/dL)	51 ± 4.4 [45]	58.3 ± 3.7 [55]	.1
Ferritin at admission (mg/dL)	53.6 ± 10.5 [31.7]	64.4 ± 7 [56.1]	.4
Estimated blood loss (cc)	440.3 ± 28.9 [400]	460 ± 29 [400]	.61
Fluids delivered (cc)	4177 ± 226 [4000]	4234 ± 153 [4250]	.8
Urine output (cc)	1110 ± 137 [1000]	777 ± 88 [625]	.05

Mean ± SE [median] values.

Table 3. TRANSFUSION DATA

	Patients Transfused Intraoperatively	Blood Units (intraop)	Patients Transfused Postoperatively	Blood Units (postop)
Study group (n = 31)	9 (29%)	20	1 (3.2%)	2
Control group (n = 32)	19 (59.3%)	46	9 (28%)	14
All patients (n = 63)	28 (44.4%)	66	10 (15.8%)	16

Clinicopathological data are depicted in Table 1. Hematologic profiles at admission revealed no significant differences between the two groups (Table 2). Comparable hemoglobin and hematocrit values at admission and comparable fluid administration and losses at operation indicate similar transfusion status for both groups.

Operative and Postoperative Transfusions

During operation, 28 (44.4%) patients were transfused because of intraoperative blood loss (10 of them were also transfused postoperatively) with a hemoglobin level of less than 8.5 g/dL. Of these, nine patients (29%) who received transfusions (total of 20 units of packed red blood cells) had received erythropoietin preoperatively. Nineteen patients (59.3%) who did not receive erythropoietin before surgery were also transfused (total of 46 units of packed red blood cells). The difference in the operative transfusion rate between the study and the control group was statistically significant (9 patients with a total of 20 units vs. 19 patients with a total of 46 units; $P = .023$). In addition, during the postoperative period a markedly increased number of patients (n = 9 [28%]) from the control group received an allogenic transfusion compared to only one patient (3.2%) in the study group who was transfused ($P = .001$) (Table 3).

Hemoglobin and Reticulocyte Counts in Study Group

A statistically significant increase in hemoglobin levels between study onset and the operation was observed in the erythropoietin group ($P = .01$). A similar increase in hemoglobin values in patients treated with erythropoietin was observed between the initiation of the treatment and the seventh postoperative day ($P = .01$), as well as between the operation day and the seventh postoperative day ($P = .02$) (Fig. 1). To investigate whether this increase was due to stimulated hematopoiesis, the course of reticulocyte counts was analyzed, and a comparable highly significant increase was detected between the day of study onset and the seventh postoperative day in the study group ($P = .0001$) (Fig. 2).

Comparison of Hematocrit, Hemoglobin, and Reticulocyte Counts in the Two Groups

An increase in preoperative hematocrit and hemoglobin values was detected in the treatment group compared to the placebo group, but it was not statistically significant ($P > .05$). However, in the postoperative period, the mean hemoglobin and hematocrit values in erythropoietin-treated patients were consistently higher compared to patients in the control group. Significant differences in the mean hemoglobin and hematocrit values between the two groups were observed at the third ($P = .04$, $P = .01$), fifth ($P = .04$, $P = .04$), and seventh ($P = .003$, $P = .001$) postoperative days (see Fig. 1). Significant differences in reticulocyte values, the major marker of stimulated hematopoiesis, were also observed between the two groups on the fifth ($P = .008$) and first ($P = .001$) preoperative days as well as on the fifth ($P = .002$) and seventh ($P = .001$) postoperative days (see Fig. 2). Transfusion data of patients at discharge are presented in Table 4.

Outcome of Patients

Twenty patients (31.7%) experienced postoperative complications, such as anastomotic leak (1 [1.6%]), abscess/fistula formation (1 [1.6%]), hemorrhage (5 [7.9%]), wound infection (6 [9.5%]), pulmonary complications (4 [6.3%]), and complications from blood transfusions (3 [4.8%]).

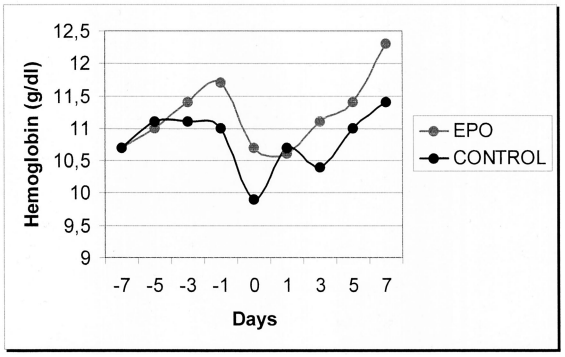

Figure 1. Hemoglobin levels in patients receiving erythropoietin and placebo regimens. Day 0: Day of operation for cancer of the gastrointestinal tract.

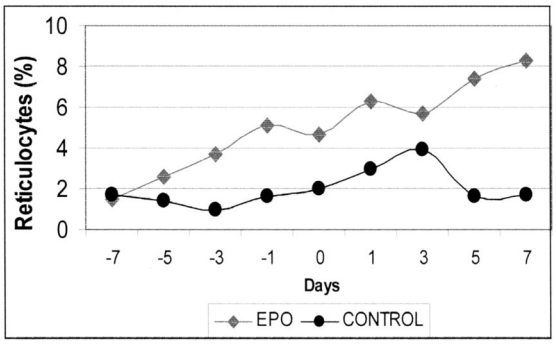

Figure 2. Reticulocyte (%) levels in patients receiving erythropoietin and placebo regimens. Day 0: Day of operation for cancer of the gastrointestinal tract.

Table 5. MULTIVARIATE ANALYSIS OF PROGNOSTIC FACTORS

Variable	Exp (B)—95% CI	*P* Value
Age	1.04–0.98/1.1	.12
Sex	0.41–0.091/1.9	.25
Stage	0.69–0.039/12.25	.81
Tumor location	0.18–0.01/2.63	.58
Postoperative complications	0.52–0.15/1.78	.3
Transfusions	0.73–0.21/2.57	.63
Epoietin treatment	0.21–0.052/0.91	.03

Data are given as prognostic factors for 1-year survival.

Complications were mostly observed in patients who did not receive erythropoietin treatment (n = 13 [40.6%] vs. n = 4 [12.9%]) ($P = .02$). Additionally, patients receiving transfusions had a higher complication rate (n = 13 [46.4%]) compared to the control group (n = 4 [11.4%]) ($P = .004$). Furthermore, the duration of hospitalization was significantly increased in the control group (13 ± 0.9 days vs. 10 ± 0.5 days; $P = .022$).

The 1-year survival rate was found to be significantly higher in patients receiving erythropoietin treatment (80.6% vs. 59.3%, $P = .04$). In a multivariate model of analysis, we evaluated the impact of erythropoietin treatment on the survival of patients with gastrointestinal cancer and found that the use of erythropoietin improves the outcome of operated cancer patients (Table 5).

Side effects possibly attributable to erythropoietin were observed in five cases. Three patients reported mild and transient hypertension and two clinical deep venous thrombosis. Still, there were also two patients in the control group with mild hypertension and one with deep venous thrombosis. Those events were considered by the investigators as unrelated to the administration of the studied drug. No major allergic reactions were reported.

DISCUSSION

Anemia is common in cancer patients, although the prevalence is influenced both by the type of malignancy and the choice of treatment. In most cases it is a mild to moderate, hyporegenerative anemia with a relatively reduced reticulocyte count, a process in which erythropoietin and iron play prominent causative roles.[12]

Most anemic patients with cancer of the gastrointestinal tract have iron deficiency due to subclinical blood loss; therefore, an iron supplement has been advocated.[2,13] Still, iron supplementation has not been found to be able to stimulate erythropoiesis to a sufficient degree to facilitate autologous blood donation or to reduce the need for allogenic blood transfusions in cancer patients.[2] This could be due to a reticuloendothelial blockage of iron, characteristic of several other conditions seen in these patients.[12]

The percentage of patients transfused differs widely among various centers, ranging from 0% to 78%.[14] The overall risk associated with transfusions of heterologous blood has been reduced due to extensive laboratory testing, but recipients are still at risk for transfusion reactions, transmission of unknown diseases, and immunosuppression. Furthermore, the number of transfusions is believed to be associated with worse prognosis in cancer patients.[5,15–17]

Several studies have examined the yield of autologous predonated blood following erythropoietin administration. In the study by Braga et al., preoperative erythropoietin treatment was found to facilitate autologous blood donation in anemic patients with cancer of the gastrointestinal tract, resulting in a reduction of perioperative homologous blood transfusions.[2] Still, the delay in the time of operation of cancer patients prohibits its widespread use.

Table 4. HEMATOLOGIC PROFILE AT DISCHARGE

	Study Group	Control Group	*P* Value
Hemoglobin at discharge (g/dL)	12.1 ± 0.16 [12.2]	11.1 ± 0.15 [11.2]	.0001
Hematocrit at discharge (%)	37.8 ± 0.5 [37.5]	34.8 ± 0.37 [34.7]	.0001
Reticulocytes at discharge	8.4 ± 0.37 [8]	1.7 ± 0.26 [1.2]	.0001
Iron at discharge (mg/dL)	102 ± 8.4 [107]	101 ± 6.7 [103]	.9
Ferritin at discharge (mg/dL)	350 ± 50.5 [386]	355 ± 52.5 [386]	.9

Mean ± SE [median] values.

This randomized double-blind study has demonstrated that supplementing erythropoietin and iron for at least 14 days can stimulate the hematopoiesis of patients with gastrointestinal tract cancer–induced anemia. We administered iron intravenously to obtain the full effect of erythropoietin, as recommended in patients with a baseline serum ferritin of less than 100 ng/mL.[18] The dependency of the hemoglobin response on iron availability indicates a potential therapeutic synergism of intravenously administrated iron and erythropoietin.[19]

An increase in the doses of erythropoietin (20,000 units) offers a further possibility for enhancing the effectiveness of erythropoietin because it is not the peak but the maintenance of its blood levels that seems to be the major determinant of its efficiency.[20]

A cost-effectiveness analysis may be difficult to perform because the costs of the potential risks from blood transfusions are difficult to calculate and the cost of erythropoietin may not be so expensive, considering the benefits of the treatment. The cost of allogenic transfusion in our hospital is estimated at 400 euros per unit. Conversely, the administration of erythropoietin costs 180 euros per day (supplemental iron administration: 20 euros per day), and it was found to be related to a lower postoperative complication rate and better survival outcome. We demonstrated that allogenic transfusions were associated with an increased number of postoperative complications, leading to a longer hospital stay. The daily cost of hospitalization is 400 euros. Although erythropoietin administration costs more than expected, an uncomplicated postoperative period and better survival time cannot be calculated in a simple cost/benefit equation. Furthermore, in patients who consider blood transfusions to be unethical for religious reasons, erythropoietin administration represents the only alternative.

This study showed that short-term perioperative administration of recombinant human erythropoietin decreases the need for allogenic blood transfusions in anemic patients undergoing surgery for gastrointestinal tract cancer. Erythropoietin also appears to be associated with a favorable complication and survival outcome for these cancer patients.

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